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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/821,813 | 04/08/2004 | Thomas A. Boyd | P0453.70112US01 | 9059 |

75482 7590 11/19/2009

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| EXAMINER | |
|---|---|
| SPIVACK, PHYLLIS G | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 11/19/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/821,813 | BOYD ET AL. | |
| | Examiner | Art Unit | |
| | Phyllis G. Spivack | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *2, 4-10, 12, 12, 33, 35, 36, 40, 48-50, 71-75, 78, 79, 91-94, 98, 100-102, 105 and 106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,11,14-18,21-32,38,39,43,45,51-61,64-70,76,77,82-85,88,95,96,103,104,107-109 and 112-121.

Continuation of Disposition of Claims: Claims rejected are 1,11,14-18,21-32,38,39,43,45,51-61,64-70,76,77,82-85,88,95,96,103,104,107-109 and 112-121.

Applicants' Response filed July 13, 2009 is acknowledged. Claims 2, 4-10, 12, 13, 33, 35, 36, 40, 48-50, 71-75, 78, 79, 91- 94, 98, 100-102, 105 and 106 remain withdrawn from consideration. Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 remain under consideration.

Applicants' arguments have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are reiterated. They constitute the complete set presently applied to the instant application.

In the last Office Action claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 were rejected under 35 U.S.C. 103(a) as being unpatentable over Minoia et al., U.S. Patent 5,811,451. It was asserted Minola teaches the administration of methylnaltrexone along with calcium salts to treat irritable bowel syndrome (IBS). See column 3, lines 17 and 63-64. According to Minoia, methylnaltrexone is among those opiate antagonists that may be administered to treat an endorphin-mediated pathology, such as IBS. See claims 1 and 2, columns 7-8. Minoia states the choice of the opiate antagonist is within the purview of those skilled in the art based on kinetics, potency, safety, pharmacological risks, etc. See column 3, lines 47-50.

Applicants argue one of ordinary skill in the art would have been looking for centrally acting drugs to treat irritable bowel syndrome. Applicants further argue Minoia does not specifically single out or suggest a peripheral opioid antagonist, such as methylnaltrexone, as a candidate for the treatment of irritable bowel syndrome.

Applicants' argument is not found persuasive. The rejection of record of claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 under 35 U.S.C. 103(a) as being unpatentable over Minoia et al., U.S. Patent 5,811,451, is maintained. According to Minoia, irritable bowel syndrome is an endorphin-mediated pathology that may be treated by administration of an opiate antagonist such as methylnaltrexone.

Claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 were also rejected under 35 U.S.C. 103(a) as being unpatentable over Rhodes et al., S.S. Patent 6,734,188, in view of Drell et al., WO 99/22737, in the last Office Action. It was asserted Rhodes teaches the administration of an effective amount of any opioid antagonist to treat irritable bowel syndrome. See claims 15-17, column 8. Rhodes includes any pharmacologically acceptable derivative of opioid antagonists that exhibit the same type of pharmacological activity as those specifically exemplified in his teaching. Motivation to administer methylnaltrexone flows from Drell's teaching. See page 2, lines 21-25. Methylnaltrexone does not cross the blood brain barrier because it is a quaternary amine with a relatively higher polarity and reduced lipid solubility when compared to tertiary forms of opioid antagonists. Drell further teaches various dosage forms, as well as the additional administration of an opioid, in the Abstract. See page 6, lines 16-20, where dosages of methylnaltrexone are disclosed.

Applicants argue Rhodes focuses on centrally acting opioid antagonists. Applicants provide a copy of Brown et al., Neuropharmacology, to support a lack of

pharmacological effect for quaternary compounds for opiate receptors. From this reference Applicants argue "...quaternization of the opiate antagonists generally greatly diminished their affinity for opiate receptors. Methylnaloxone has generally been found to posses only 2 to 4% of the opiate antagonist activity of naloxone *in vitro* and potency differences between methylnaltrexone and naltrexone are of the same order. Applicants urge Brown states ".. [a] seeming lack of pharmacological effect may be due to the relatively low affinity of these quaternary compounds for opiate receptors."

Applicants' argument is not found persuasive. The rejection of record of claims 1, 11, 14-18, 21-32, 38, 39, 43, 45, 51-61, 64-70, 76, 77, 82-85, 88, 95, 96, 103, 104, 107-109 and 112-121 under 35 U.S.C. 103(a) as being unpatentable over Rhodes et al., U.S. Patent 6,734,188, in view of Drell et al., WO 99/22737, is maintained.

Rhodes teaches the targeted administration of an effective amount of any opioid antagonist to treat constipation-dominant irritable bowel syndrome wherein the antagonist is released in a sustained manner in the mid- to distal small intestine or ascending colon, in claim 15, column 8. Because methylnaltrexone does not cross the blood brain barrier, the appearance of adverse effects is greatly diminished. Rhodes' disclosure includes treatment of constipation via administration of methylnaltrexone in column 2, lines 20-30. Brown's disclosure, as cited *supra*, is limited to an *in vitro* showing. Administering methylnaltrexone reduces the occurrence of side effects that occur following administration of centrally acting agents.

No claim is allowed.

**THIS ACTION IS MADE FINAL**. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this Final Action is set to expire THREE MONTHS from the mailing date of this Action. In the event a first reply is filed within TWO MONTHS of the mailing date of this Final Action and the Advisory Action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the Advisory Action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the Advisory Action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this Final Action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

November 17, 2009

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614